REMARKS

Claims 34, 41-43,45, 48-52 and 54 are pending in this application. Claims 35-40, 44, 46, 47, 53 and 55 have been canceled.

The Office Action of May 24, 2001 presents the examination of claims 34-52, claims 53-55 being withdrawn from consideration.

An interview with the Examiner was conducted on October 5, 2001. The assistance of the Examiner in advancing prosecution of the application is much appreciated.

Rejoinder of method of use claims requested

Claim 54 stands withdrawn from consideration. Applicants submit that this claim is directed to methods of use of the composition of matter described in the other pending claims and are commensurate in scope with those claims. Claim 54 is a method of use claim that was not present at the time of restriction of the application in paper 13, mailed August 9, 2000.

The Examiner has not shown that the process of use of the composition as recited in claim 54 can be performed independently of the elected product claim. Furthermore, claim 54 is explicitly dependent upon one (claim 52) of the elected and examined claims. *See*, M.P.E.P. §§ 806.05(h), 809, 809.03

and 821.04. Accordingly, claim 54 should be rejoined and found allowable upon allowance of the presently pending claims 34, 41-43, 45 and 48-52.

In the interview of October 5, the Examiner agreed to consider this matter upon allowance of a composition claim.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 34-52 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description of the claimed subject matter in the specification. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner describes several bases for this rejection. First, he indicates that the term "comprising" allows the attachment of unknown nucleotide sequences to either end of any particular recited sequence or within the recited sequence. Second, the Examiner describes the term "semaphorin domain" as being ill-defined in the specification, in that the structural determinants of a semaphorin domain are not sufficiently described that one of ordinary skill in the art can recognize such a domain. Third, the Examiner takes a position that the structural features of a semaphorin domain that are responsible

for function of a semaphorin W protein are not described in the specification. Applicants address each of these issues below.

First, the term "semaphorin domain" has now been deleted from the claims. Thus, the Examiner's concerns about the features that define a semaphorin domain, and the function thereof, are now irrelevant. As to the term "comprising", Applicants explained in the October 5 interview that this term should not be problematic for the reasons explained below. The Examiner agreed to this in principle.

The present claims and specification are written in terms consistent with claims deemed supported by adequate written description in the "Revised Interim Written Description Guidelines Training Materials" (http://www.uspto.gov/web/offices/pac/writtendesc.pdf, hereinafter "the Training Materials"). It appears that the Examiner has tried to compare the present specification and claims with the Examples provided in these materials, but has looked to the wrong examples, perhaps due to confusion about what is disclosed and claimed in the present application.

The language of the Office Action suggests that the Examiner is relying upon Example 7 of the Training Materials. Example 7 relates to disclosure of merely an

EST sequence, i.e. a short nucleotide sequence that is only a short portion of a cDNA and might or might not include a part of the amino acid-encoding part of the cDNA. In Example 7, a claim reading, "An isolated DNA comprising SEQ ID NO: 16" is deemed not supported by the specification. This is because the written description fails to provide any information about the coding capacity of any cDNA molecule. There is deemed to be no description of the genus of DNAs that include SEQ ID NO: 16 as a part of their sequence, thus use of the transitional phrase "comprising" is deemed inappropriate.

On the other hand, the present application includes much more than merely an EST sequence. A complete sequence of a cDNA encoding rat semaphorin W is disclosed. (SEQ ID NO: 1) The cognate protein is expressed in a mammalian cell and the expressed protein is shown to have two of the biological activities expected for a semaphorin protein. (See Examples 7-9 at page 58.) Structural features of a semaphorin protein are described. (See page 23, lines 9-25.) A second species, human semaphorin W, is isolated using the disclosed rat nucleic acid, and is characterized as to most of its sequence. (Example 4 at page 54 and SEQ ID NOs 4 and 10.) Thus, the applicable examples from the Training Materials are Examples 8, 9 and 14.

Claim 1 in Example 8 recites, "An isolated and purified nucleic acid comprising SEQ ID NO: 2." (Compare to the instant claim 34). The exemplified disclosure of the specification is a complete open reading frame cDNA (cf. SEQ ID NO: 1 of the instant application) encoding an amino acid sequence (cf. SEQ ID NO: 3 of the instant application). A certain, albeit not particularly high, level of sequence conservation of the encoded protein with a protein of a known function is disclosed (cf. homology to semaphorin proteins of the instant application at pages 19-20). The Training Materials specifically indicate that,

> One of skill in the art can readily envisage nucleic acid sequence which include SEQ ID NO: 2 because e.g. SEQ ID NO: 2 can be embedded in known vectors. Although there may be substantial variability among the species of DNAs encompassed with the scope of the claim because SEQ ID NO: 2 may be combined with sequences known in the art, e.g. expression vectors, the necessary common attribute is the ORF (SEQ ID NO: 2).

Thus, claim 34 at least should be deemed to be supported by adequate written description in the specification.

Example 9 of the Training Materials addresses claims that recite the invention in terms of hybridization to a

reference sequence. Thus, Example 9 is relevant to the instant claims 41 and 42.

The claim in Example 9 states:

> An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.

This claim language is identical in its general content to that of the present claims 41 and 42. The hybridization conditions set forth in the instant claims[1] are considered to be highly stringent in the art as shown by Exhibit 5, attached[2]. A reference sequence is set forth. A biological activity of a protein is set forth.

The disclosure in the instant specification is also almost identical to that in Example 9. There is at least one cDNA disclosed that encodes a protein that has the biological activity recited in the claims. The specification includes an example wherein the reference

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[1] See, page 20, lines 7-9 of the specification.

[2]The conditions recited in the claims are equivalent to hybridization at 65 °C in an aqueous buffer, indeed they provide a higher stringency. Note that the equation on p. 9.51 of Exhibit 5 the inclusion of 45% formamide lowers the Tm by 28 °C. Thus, the buffer conditions recited in the present claims provide stringency equivalent to hybridization in aqueous solution at a temperature of about 37 °C, and the use of 42 °C as the hybridization temperature provides even greater stringency.

sequence was used under the recited hybridization conditions to isolate an additional clone. While the additional clone has not been shown to be functional, nucleotide sequence characterization was performed. The isolated clone exhibits a sequence from which the skilled artisan would conclude that the human homolog of the rat semaphorin W had been obtained. (See page 55, lines 1-8, of the specification.)

In the interview of October 5, the Examiner requested that Applicants provide an alignment of the human and rat Semaphorin W sequences and an indication of the degree of overall identity between them.

The Examiner is referred to Exhibit 1 filed with Applicants' previous response for orientation. Exhibit 1 shows the relationship of the N-terminal and C-terminal sequences (both nucleic acid and amino acid) of the human Semaphorin W cDNA clone described in the application to the rat Semaphorin W sequences described in the application. The bottom of the figure shows that a single cDNA was obtained that included the N-terminal and C-terminal sequences as a contiguous sequence. Compared to the rat sequence, there was an internal gap and also, though the DNA encoding the initiator methionine is found, the extreme N-terminus of the human sequence was absent. The presence of the internal gap indicates that the obtained human sequence is a splicing variant of the rat sequence as defined by SEQ ID NOs: 1 and 2.

Exhibit 6 attached hereto shows the alignment of the human and rat Semaphorin W nucleotide sequences for the N-terminal portion of the cDNA; the degree of sequence identity is 82.8%. Exhibit 7 shows the corresponding alignment of the amino acid sequences; the degree of sequence identity is 80.6%. Exhibit 8 shows the alignment of the human and rat Semaphorin W nucleotide sequences for the C-terminal portion of the cDNA; the degree of sequence identity is 87.7%. Exhibit 9 shows the alignment of the

corresponding amino acid sequences; the degree of sequence identity is 92.6%.

Recently the sequence of a variant of the human Semaphorin W cDNA that includes the portion represented by the internal gap shown in Exhibit 1 has become available. Exhibit 10 is an alignment of the nucleotide sequences of the human and rat Semaphorin cDNAs that include this portion; the overall degree of sequence identity is 82.4%. Exhibit 11 is an alignment of the corresponding amino acid sequences; the overall degree of sequence identity is 90.6%.

Thus, the instant claims 41 and 42 should be deemed adequately described by the instant specification.

The instant claims 43 and 45 recite the claimed invention in terms of a degree of sequence identity to a reference sequence together with a biological activity of the encoded protein. In the case of these claims, the relevant example from the Training Materials is Example 14.

Example 14 is written in terms of a protein invention, but the language of the claim is such that it is clear that the teachings of the example are applicable to the instant claims 43 and 45. As in Example 14 of the Training Materials, Applicants have argued that the methods for making variant nucleic acids within the scope of claims 43

and 45 were well-known in the art at the time the instant application was filed. This is expressly stated in the specification at page 14, lines 11-24. Furthermore, expression of a protein encoded by the nucleic acids of the invention is shown in a working Example (Example 7) and testing of the expressed protein for biological activity is described in further working examples (Examples 8 and 9). Thus, "an assay is described which will identify other proteins having the claimed [catalytic] activity".

The degree of sequence identity recited in the present claims is a bit lower than that in Example 14 of the Training Materials (80% cf. 95%). However, Applicants submit that the lower degree of identity is supportable in view of the inclusion of a two species of nucleic acid sequences having a degree of identity falling within the limits recited in the claims. Also, the specification describes a number of attributes of the nucleic acids of the present invention in addition to the minimal description set forth in Example 14. For instance, the specification describes the encoded protein as one that includes a semaphorin domain, which is in turn described in fair detail at pages 23-24 of the specification. A conserved glutamic acid residue (no. 204 in SEQ ID NO: 3) is also indicated and stated to be possibly substitutable

by aspartic acid. Furthermore, the specification indicates at page 20, lines 18-21 that the degree of sequence variation among avian and mammalian semaphorin W genes is typically more than 80%. Thus, the skilled artisan is directed to sources of nucleic acids that would fall within the scope of the present claims.

In Example 14 of the Training Materials, a claim encompassing proteins that are variants of a recited sequence and have a stated catalytic activity were deemed adequately described. As the instant claims 43 and 45 and the present specification are both analogous to the disclosure and claims presented in Example 14 of the Training Materials, these claims must be deemed adequately described by the specification.

The Examiner has not expressed any other bases for rejection of other claims in the application. Thus, for the reasons explained above, claims 34, 41-43, 45 and 48-52 should be found adequately described in the present specification and the instant rejection should be withdrawn.

Enablement

Claims 34-52 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement by the

specification. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner provides a very detailed explanation of his position at pp. 9-14 of the Office Action. It appears that his position can be distilled to two thoughts. First, it seems that the Examiner asserts that the claims as presented previously encompass proteins encoded by partial cDNAs (i.e. cDNAs that do not encode a complete protein, SEQ ID NOs: 4, 5, 7 and 10). Thus, the Examiner believes it would be undue experimentation for one of ordinary skill in the art to "fill in" the gaps in the sequences to produce a complete cDNA that encodes a functional protein. Second, the Examiner asserts that one of ordinary skill in the art cannot predict *a priori* if any particular variation of the amino acid sequence of SEQ ID NO: 3 would have the biological activities stated in the claims.

With respect to the first basis for the rejection, the claims as amended no longer recite the partial cDNA sequences of SEQ ID NOs 4, 5, 7 and 10. Only complete coding sequences are recited as reference sequences in the claims. All of the claims recite that the protein encoded has one or another of two biological activities observed for a protein having the amino acid sequence of SEQ ID NO: 3.

Applicants have previously presented their view of the so-called "Wands" factors to be considered in weighing enablement. The Examiner does not provide any substantial rebuttal of these arguments, instead merely stating in a conclusory manner that "unpredictability of biological function of a protein alone could render one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed." The Examiner's further statements at page 14 of the Office Action also rely strongly upon the alleged unpredictability of the art. The Examiner also makes a statement that the unpredictability is rooted in a lack of knowledge of structure-function relationships as to the determinants of semaphorin W activity.

As a threshold matter, Applicants wish to clarify that the Examiner's arguments do not seem to apply to claims 51 and 52. These claims recite nucleic acids representing portions of specific sequences. There is no "unpredictability" with respect to the structure of the nucleic acids of these claims. The nucleic acids of these claims have utility as research tools or diagnostic probes as disclosed in the specification. Thus, the instant rejection would seem not to be applicable and should be withdrawn as to claims 51 and 52.

As to the remaining claims, Applicants stand by their detailed arguments on enablement of the invention presented in their paper of March 28, 2001.

Applicants would point out that the "invention as claimed" no longer recites proteins encoded by nucleic acids comprising partial cDNAs. This clarifies the claim language a bit, but is not a narrowing of the scope of the claims, as the claims were always limited to embodiments that encoded a functional protein.

As to the Examiner's reliance on the "unpredictability" factor, Applicants first reiterate that an argument for lack of enablement solely based upon unpredictability in the art does not establish undue experimentation is required to practice the invention. Additional factors must be considered and weighed.

Applicants again point out that, other than claims 51 and 52, the present claims do not encompass embodiments of the invention that lack the biological activities stated in the claims.

Applicants again assert that one of ordinary skill in the art can readily utilize the cloned DNAs deposited by the inventors as starting materials to perform mutation and screening experiments by methods known in the art and described in detail in the specification. The need for such

screening to address the lack of ability to predict *a priori* what changes to the basic structure can be tolerated is expected by the skilled artisan. Furthermore, it is quite predictable that variants of sequences recited in the claims that represent functional embodiments will be isolated by such an approach. Thus, as explicitly held in the *Wands case*, this sort of mutation-screening approach to identifying additional embodiments of the invention is not undue experimentation. The Examiner is reminded that the practitioner in the *Wands* case could not predict *a priori* which particular hybridoma secreted a functional antibody. Furthermore, the success rate for the screening for hybridomas described in the *Wands* case was a mere 2.8% and that only 2 of 10 experiments succeeded at all. Nonetheless, the Federal Circuit found that the experimentation described in that case was not undue.

For the reasons stated above and in Applicants' paper of March 28, 2001, Applicants submit that the present specification fully enables practice of the claimed invention and the instant rejection should be withdrawn.

Rejections over prior art

Claims 51 and 52 stand rejected over Hillier et al., GENBANK Accession No. H24181. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The present claims 51 and 52 specifically exclude the nucleotide sequences of GenBank Accession No:T09073 or GenBank Accession No:R54387. H24181 is a sequence entirely included within R54387. (See, Exhibit 12.) Thus, H24181 is also excluded from claims 51 and 52. Accordingly, the instant rejection should be withdrawn.

Claims 51 and 52 also stand rejected over Igarashi et al., GENBANK Accession No. Q56609. Claim 51 recites SEQ ID NOs: 2, 4 or 10. SEQ ID NO: 2 is the coding portion of the cDNA encoding rat Semaphorin W and constitutes residues 76 to 2406 of SEQ ID NO: 1, which is the complete rat Semaphorin W cDNA. Q56609 in the C-terminal non-coding portion of the rat Semaphorin W cDNA (residues 3355-3402 of SEQ ID NO: 1) and is thus not included in SEQ ID NO: 2. Thus, the present claims 51 and 52 do not include Q56609 and the instant rejection should be withdrawn.

Applicants submit that the present application well-describes and claims patentable subject matter. The favorable action of allowance of all of the pending claims is

respectfully requested. If there are any minor matters precluding allowance of the application which may be resolved by a telephone discussion, the Examiner is respectfully requested to contact Mark J. Nuell, Ph.D. (Reg. No. 36,623) at (703) 205-8000.

Pursuant to 37 C.F.R. § 1.17 and 1.136(a), Applicants respectfully petitioned for a three (3) month extension of time for filing a response in connection with the present application in the Request for Contiued Examination filed concurrently herewith. The required fee of $920.00 is attached thereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Attached hereto is a marked-up version of the changes made to the application by this Amendment.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Mark J. Nuell, #36,623

DRN/KLR:bmp
0020-4546P

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

Attachment: Version with Markings to Show Changes Made
Exhibits 5-12

(Rev. 09/26/01)

Version Showing Changes Made

Claims 35-40, 44, 46, 47, 53 and 55 are canceled. The remaining pending claims are amended as shown below.

34. (Amended) An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO:1;

(b) the nucleotide sequence of SEQ ID NO:~~1~~2 ~~from nucleotide 76 to nucleotide 2406~~; and

~~(c) the nucleotide sequence of SEQ ID NO:4;~~

~~(d) the nucleotide sequence of SEQ ID NO:4 from nucleotide 1 to nucleotide 1761;~~

~~(e) the nucleotide sequence of SEQ ID NO:10;~~

~~(f)~~(c) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:3~~;~~

~~(g) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:6; and~~

~~(h) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:11~~.

41. (Amended) An isolated nucleic acid molecule comprising a polynucleotide that specifically hybridizes

with a polynucleotide having a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO:1; and

(b) the nucleotide sequence of SEQ ID NO:~~1~~2 ~~from nucleotide 76 to nucleotide 2406~~;

~~(c) the nucleotide sequence of SEQ ID NO:4;~~

~~(d) the nucleotide sequence of SEQ ID NO:4 from nucleotide 1 to nucleotide 1761; and~~

~~(e) the nucleotide sequence of SEQ ID NO:10;~~

under conditions of a buffer comprising 45%(v/v) formamide, 5x SSPE, at 42°C, and washing after hybridization with a buffer comprising 2xSSPE at 42°C, and that encodes a protein having the biological activity of inhibiting neurite outgrowth from dorsal root ganglion cells.

42. (Amended) An isolated nucleic acid molecule comprising a polynucleotide that specifically hybridizes with a polynucleotide having a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO:1; and

(b) the nucleotide sequence of SEQ ID NO:~~1~~2 ~~from nucleotide 76 to nucleotide 2406~~;

~~(c) the nucleotide sequence of SEQ ID NO:4;~~

~~(d) the nucleotide sequence of SEQ ID NO:4 from nucleotide 1 to nucleotide 1761; and~~

~~(e) the nucleotide sequence of SEQ ID NO:10;~~

under conditions of a buffer comprising 45%(v/v) formamide, 5x SSPE, at 42°C, and washing after hybridization with a buffer comprising 2xSSPE, at 42°C, and that encodes a protein having the biological activity of collapsing growth cones of retinal ganglion cells.

43. (Amended) An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence that has 80% or more sequence identity with a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO:1;

(b) the nucleotide sequence of SEQ ID NO:~~1~~2 ~~from nucleotide 76 to nucleotide 2406~~; and

~~(c) the nucleotide sequence of SEQ ID NO:1 from nucleotide 259 to nucleotide 1776;~~

~~(d)~~(c) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:3; ~~and~~

~~(e) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:3 from amino acid 62 to amino acid 567;~~

~~and~~ that encodes a protein having the biological activity of inhibiting neurite outgrowth from dorsal root ganglion cells.

45. (Amended) An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence that has 80% or more sequence identity with a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO:1;

(b) the nucleotide sequence of SEQ ID NO:~~1~~2 ~~from nucleotide 76 to nucleotide 2406~~; and

~~(c) the nucleotide sequence of SEQ ID NO:1 from nucleotide 259 to nucleotide 1776;~~

~~(d)~~(c) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:3; ~~and~~

~~(e) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:3 from amino acid 62 to amino acid 567;~~

~~and~~ that encodes a protein having the biological activity of collapsing growth cones of retinal ganglion cells.

48. (Amended) An expression plasmid comprising the nucleic acid molecule of claim 34, ~~35, 36, 37, 38, 39, 40,~~ 41, 42, 43~~, 44,~~ or 45~~, 46, or 47~~.

51. (Amended) An isolated nucleic acid molecule ~~comprising~~ consisting of a polynucleotide ~~having a sequence of 27 or more~~ consisting of at least 27 contiguous nucleotides of SEQ ID NO:~~1~~2, 4, or 10 with the ~~exception of a~~ proviso that said nucleic acid molecule ~~which consists~~ does not consist of a polynucleotide ~~having a sequence of 27 or more~~ consisting of at least 27 contiguous nucleotides disclosed in GenBank Accession No:T09073 or GenBank Accession No:R54387.